Biophysical Characterization of Arc: Insights into Learning and Memory

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Neuroplasticity is thought to be critical for learning and memory storage. Such a process relies on changes in neural pathways and synapses. AMPA-type glutamate receptors (AMPARs) on dendritic surface mediate fast synaptic transmission in the CNS. Neuronal plasticity mechanisms such as Long-Term Potentiation (LTP) and Long-Term Depression (LTD) are dependent on the localized expression of Immediate Early Genes (IEG). Arc is an IEG, whose mRNA is trafficked to dendrites and accumulates at the site of synaptic activity where it is synthesized locally and has been shown to regulate AMPARs expression on the Plasma Membrane. Arc has also been shown to interact with dynamin (Dyn2) to mediate the number of surface proteins by way of clathrin endocytosis. For this study, bacterially expressed proteins, His-PICK1, GST-Arc, and Dynamin 2, were characterized for their potential interaction. Recombinant Arc's interactions with Dyn2 were quantified with the use of turbidity assays. Self-association of Arc, which we predict to be of critical important for interaction with Dyn2, was characterized with fluorescence polarization assays and size-exclusion chromatography. Furthermore, the experiment isolated a binding partner of Arc that directly associates with AMPARs, namely PICK1, through pull-down assays of neuronal lysates. These findings give credence to the C-kinase 1 (PICK1)/AMPAR complex as the structure to which Arc binds to selectively target Dyn2 to traffic AMPARs in order to facilitate synaptic neuronal plasticity. Expansion of this project includes characterizing the interaction of Arc, PICK1, and Dyn2 on model membrane systems in vivo and in live cells.

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